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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,977	02/26/1999	JAMES M. WILSON	GNVPN.019BUS	1765

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/242,977	WILSON ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-24,26-28 and 30-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-24,26-28 and 30-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/21/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response filed 9-26-2003 has been received and entered.

2. Claims 19-24, 26-28 and 30-38 are pending and are instantly under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 19-24, 26-28 remain rejected and claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record set forth in the previous office action of 11-23-01, 7-22-02 and 3-27-03.

Response to Arguments

Applicant's arguments filed 9-26-2003 have been fully considered but they are not persuasive. Applicants argue that page 35, lines 1-5 describe as to how the rAAV preparation is purified and describe a method of detecting the amount of contamination. However, these arguments are not persuasive because teaching a method to detect contamination or purify does not teach what contamination will be in a preparation or how pure a composition is.

3. Claims 19-24 and 26-28 remain rejected and claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a recombinant adeno-associated virus (rAAV suspended in a biological compatible carrier, wherein the rAAV comprises (i) a 5'

AAV inverted terminal repeat (ITR), (ii) a nucleic acid sequence encoding human apolipoprotein E (human ApoE) operably linked to a eukaryotic promoter, and (iii) a 3' AAV ITR, and wherein the level of contaminating adenoviral helper virus is same as that obtained by subjecting said recombinant AAV to four rounds of cesium chloride centrifugation and a method of delivering ApoE to a mammal with atherosclerosis, wherein said method comprises the step of administering to the mammal intramuscularly the composition comprising the rAAV and wherein the ApoE encoding sequence in the composition is expressed in the mammal and wherein a cytotoxic immune response directed against rAAV-transduced cells of the mammal expressing ApoE is absent in the mammal, does not reasonably provide enablement for any and all rAAV vectors wherein the ApoE encoding sequences are not linked to a promoter or wherein multiple ITRs or multiple ApoE encoding sequences are present or wherein the contaminating levels of adenoviral helper virus are lower than the levels of contaminating adenoviral helper virus after subjecting the rAAV to four rounds of cesium chloride centrifugation or wherein the vector is administrated by any method, for reasons of record set forth in the previous office action of 11-23-01, 7-22-02 and 3-27-03. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's response filed 9-26-2003 did not contain any specific arguments regarding the issues raised in the enablement rejection.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 19-24, 26-28, and claims 30-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record set forth in the previous office action of 3-27-03.

Applicant's arguments filed 9-26-2003 have been fully considered but they are not persuasive. Applicants argue that specification describe as to how the rAAV preparation is purified and describe a method of detecting the amount of contamination. However, these arguments do not address the indefinite issue discussed in the previous office action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. The obviousness-type double patenting rejection of claims 19-24 and 26-28, set forth in the previous office action of 6-21-00 over claims 1-4 of US Patent 5,866,552 is maintained and newly presented claims 30-35 are rejected for reasons of record set forth in the office action of 6-21-00, 11-23-01 and 7-22-02.

7. Claims 19-24 and 26-35 remain provisionally rejected and claims 36-38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-11 of co-pending Application No. 09/757,673 for reasons of record set forth in the office action of 11-23-01, 7-22-02 and 3-27-03. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for expressing a transgene (ApoE in the instant application) in an animal or

in a cell or in a patient by introducing a composition comprising an adeno-associated viral vector comprising a transgene (ApoE encoding transgene in the instant application) into the cell such that the transgene is expressed in the cell, wherein the adeno-associated viral vector is free of helper adenovirus contamination. It is noted that although the claims of the instant application recite characteristic of the adeno-associated viral composition as prepared by four rounds of cesium chloride centrifugation, this limitation would still encompass a composition free of helper adenovirus vector because both the applications disclose four rounds of cesium chloride gradient centrifugation for the adeno-associated virus composition. As such, the claims of the co-pending application 09/757,673 make obvious the instantly claimed method and AAV vectors comprising the ApoE gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 19-24 and 26-35 remain provisionally rejected and claims 36-38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9, 20, 21, 23, 25, 26, and 27 of co-pending Application No. 09/237,064 for reasons of record set forth in the office action of 11-23-01, 7-22-02 and 3-27-03. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for expressing a ApoE in an animal/patient by introducing a composition comprising an adeno-associated viral vector comprising ApoE transgene into the cell such that the transgene is expressed in the cell, wherein the adeno-associated viral vector is free of helper adenovirus contamination. It is noted that although the claims of the instant application recite characteristic of the adeno-associated viral composition as prepared by cesium chloride centrifugation, this limitation would still encompass a composition free of helper adenovirus vector. As such, the claims of the co-pending application

09/237,064 make obvious the instantly claimed method and AAV vectors comprising the ApoE gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Applicants' request that the double patenting rejection be deferred until allowance is acknowledged.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 19-24, 26-28 and 30-38 remain rejected and claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Podsakoff et al (US 5,858,351, 1-12-1999, filing date 1-18-1996) in view of Kaplitt et al (6,503,888, 1-7-03, effective filling date 4-13-1994) and Kashyap et al. (Ref CV of Paper No. 11).

Podsakoff et al teach a rAAV for gene therapy wherein the gene encoding erythropoietin is under the control of the CMV immediate early promoter, has SV40 polyadenylation sequences at the 3' end, and these sequences are flanked by 5' and 3' AAV ITRs (see materials and methods section in col 16 continued in col 17. They also teach that RSV promoter and other promoters can also be used for driving the expression of the gene of interest. They teach to purify the rAAV preparation by cesium chloride isopyknic gradient centrifugation and isolating the bands with average density of approximately 1.38 g/ml. Podsakoff et al also teach to inject the rAAV vector in mice intramuscularly in heart and cardiac muscles (see col 19 continued in col 20) and that erythropoietin is secreted by the myotubes or myoblasts. Podsakoff further teach that EPO gene was used as an example and

that other suitable DNA sequences could be used that encode for proteins used for the treatment of different diseases (see lines 31-67 in column 10). Podsakoff et al does not teach an rAAV vector composition comprising 5' ITR, nucleic acid sequence encoding ApoE, and 3'ITR, wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant rAAV to four rounds of cesium chloride centrifugation.

At the time of the invention, it was routine in the art to characterize an AAV preparation by histochemical staining of cells and purify the virus by multiple rounds of purification. For example, see Kiplitt et al teach the characterization by histochemical staining (example 1). Likewise, Gage and Ueba (US 6,326,484) purify their AAV by two rounds of purification (see lines 4-27 in column 28). Gage et al followed the method of Zhou et al. (J Exp. Med. 179:1867-1875, 1994).

Kashyap et al teach that genetic dyslipoproteinemias are ideal candidates for gene therapy since the molecular defects in the genes have been established and many of the diseases have significant sequelae to warrant treatment including premature cardiovascular and peripheral vascular disease or recurrent pancreatitis and pancreatic insufficiency (see the first paragraph in the section on discussion on page 1618). These investigators selected the apoE-deficient model to determine the feasibility of apolipoprotein gene replacement and prevention of atherosclerosis in mice with ApoE deficiency by providing the mice with an ApoE adenoviral vector intravenously. They also teach an ApoE adenoviral vector from which ApoE cDNA can be spliced out (see methods section on page 1613).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the rAAV vector of Podsakoff et al by cloning the ApoE cDNA taught by Kashyap et al e al, produce composition of the virus, purify it by multiple rounds of cesium chloride centrifugation to remove the helper virus completely or to the level of on infectious unit per 10^9 AAV, characterize the viral preparation by histochemical staining and use the resultant composition for delivery of ApoE gene to animals with reasonable expectation of success because all the pertinent methods are taught by Podsakoff et al and the cDNA for ApoE is taught by Kashyap et al. It is noted that purifying AAV preparation free of helper virus was

routine in the art, for example, Kiplitt et al teaches that adenovirus may be removed by heat inactivation or cesium chloride gradient (see column 8, lines 60-64). Kiplitt further add "complete elimination of adenovirus was confirmed by....." (see line 37-40 in column 20).

An artisan would have been motivated to use rAAV based method for ApoE gene delivery to treat atherosclerosis because Podsakoff et all teach that rAAV vector method is unique because of its ability to transduce non-proliferating cells along with the attributes of being inherently defective and nonpathogenic and because it is art recognized that adenovirus mediated gene delivery causes immune response (see lines 50-67 in column 1 of Podsakoff et al). With regard to claim limitations directed to specific titers of rAAV, it is noted that such an embodiment is sufficiently made obvious by the cited prior art of record in light of the state of the art as well as the level of skill of those in the art with regard to optimization parameters. For example, Podsakoff et al. teach the determination of effective dose range for rAAV vectors in Example 1. In particular, in Example 4, Podsakoff et al. teach i.m. injection into mice of rAAV-hEPO at 3×10^{11} vector genomes.

It is noted that the arts of Wilson et al have different inventors than the instant application and there is no co-pendency of the cited patents and the instant application.

Regarding applicants' remarks, it is reiterated that purifying AAV preparation free of helper virus was routine in the art, for example, Kiplitt et al teaches that adenovirus may be removed by heat inactivation or cesium chloride gradient (see column 8, lines 60-64). Kiplitt further add "complete elimination of adenovirus was confirmed by....." (see line 37-40 in column 20).

Response to Arguments

Applicant's arguments filed 9-23-2003 have been fully considered but they are not persuasive to withdraw the rejection. It is noted that in view of applicants' arguments the arts by Gage and Ueba and by Wilson have been withdrawn. However, the rejection remains in effect even without these arts since the purpose of these arts was to show that at the time of the invention, it was routine to purify

an AAV preparation by multiple rounds of purification by cesium chloride gradient centrifugation. There is nothing in the claims as instantly recited that would indicate that the AAV preparation as purified by the instant application would have not been obvious to make in view of the arts of Podsakoff et al, Kaplitt et al and Kashyap since the claims of the instant application do not recite any specific contamination level of the AAV preparation.

12. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (571) 272-0548.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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